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# Solid pseudopapillary neoplasm of the pancreas: Clinical-pathological features and management, a single-center experience

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## Abstract

Solid pseudopapillary neoplasm of the pancreas is a rare tumor of low malignancy that occurs most often in females. The study describes the clinicopathologic characteristics of the tumor and common differential diagnoses. Data were collected from a prospectively maintained database. Of 1661 patients operated for pancreatic tumors between January 2001 and September 2018, 15 patients were recorded. Patients included 12 females and 3 males, median age 40 (range 10–87) years. Computed tomography or magnetic resonance imaging was diagnostic in eight patients and a preoperative biopsy in eight out of 10 patients. Median tumor size was 5 cm (range 2–16 cm), 12 tumors were in the head, six in the body, and three in the tail of the gland. All patients except one had radical resection including one with hepatic and lymph node metastases, no patient underwent oncologic treatment. All patients are alive from 17.5 to 209.4 months postoperatively and without recurrence. Radical operation is usually curative and should also be offered to patients with metastases or recurrence as oncologic treatment has limited effect.

## Keywords

Pancreas, solid pseudopapillary neoplasm, histology, immunohistochemistry, treatment

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## Introduction

The solid pseudopapillary neoplasm (SPN) of the pancreas is a rare epithelial neoplasm of unknown origin. It accounts for 2%–3% of pancreatic tumors in adults but differs from other pancreatic neoplasms by a clear preponderance in females and a low rate of malignancy.<sup>1</sup> Contrary to other pancreatic neoplasms, SPN mainly occurs in the younger age groups and occasionally in children, and it seems to have a predilection for Asian and African American women. SPN seldom metastasizes and even in disseminated cases, surgical treatment is still an option with an often favorable outcome. An increasing incidence has been recorded during the last 15 years, which most likely is due to an extended use of computed tomography (CT) scans and magnetic

resonance imaging (MRI), since many tumors are indolent and found incidentally.<sup>2</sup>

The first report of SPN is credited by Lichtenstein,<sup>3</sup> who resected a tumor of the pancreatic tail which from the

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**Table 1.** Immunohistochemical procedures.

Antibody	Antigen (Clone)	Manufacturer	Platform
Chromogranin	LK2H10	Roche™	Ventana
Synaptophysin	DAK-SYNAP	Agilent™	Omnis
Progesterone	1E2	Roche	Ventana
Vimentin	V9	Roche	Ventana
CD10	SP67	Agilent	Omnis
CD56	123C3	Agilent	Omnis
Cyclin D1	SP4-R	Roche	Ventana
β-catenin	4	Roche	Ventana
α1-trypsin	Poly	Dako	Ventana
α1-anti-chymotrypsin	Poly	Dako	Ventana

description could have been a pseudopapillary tumor. However, the pathology was first thoroughly described by Frantz<sup>4</sup> in 1959, and the electron microscopic features by Hamoudi et al.<sup>5</sup> in 1970. The tumor has been referred to by several synonyms including the names of the above-mentioned pathologists, but in 1996 World Health Organization (WHO) renamed it solid pseudopapillary tumor and classified it as a borderline malignant neoplasm.<sup>6</sup>

Several publications on SPN are older reviews of earlier reported cases some with overlapping series. These studies include a considerable number of patients in whom diagnosis was made from morphology alone without the latest histologic and immunohistochemical techniques to reveal characteristic features. This is important as SPNs share radiological and pathologic resemblance with other less common pancreatic neoplasms such as neuroendocrine tumors, pancreatoblastomas, and acinic cell tumors. Therefore, large scale studies, although impressive in number of patients, may include an unknown amount of cases with other tumors than SPN as many of them are dated more than 50 and even 70 years back. In this study, we describe the clinics, pathology, and outcome of 15 cases of SPN that represent different clinical, radiologic, and pathologic aspects of this neoplasm.

## Patients and methods

The study was performed at a tertiary reference hospital for hepato-biliary-pancreatic (HPB) surgery with a catchment area of 2.8 million inhabitants. Data were collected from a prospectively maintained surgical database of pancreatic operations from January 2001 to September 2018.

Patients were examined according to standardized procedures. All patients had a preoperative triple-phase CT scan and if needed supplementary MRI and nuclear medicine imaging. All images were evaluated at our multidisciplinary HPB tumor conference in the presence of surgeons, oncologists, dedicated radiologists, and nuclear physicians, and resectability was assessed. Preoperative biopsies were not taken by routine, but all biopsies from other institutions were reevaluated by our pathologists.

All operations were performed as open surgery and included pancreaticoduodenectomy (Whipple's operation) for tumors in the head of the gland and a distal or left pancreatectomy with splenectomy for tumors in the body to the left of the mesenteric vessels or in the tail of the gland. Frozen section of the pancreatic resection margins was obtained in all patients to ensure tumor free margins. The surgical specimen was sent to the pathology department for final diagnosis.

Immunohistochemical studies were performed in all specimens using antibodies listed in Table 1. Formalin-fixed, paraffin-embedded samples were selected for immunohistochemical studies using respective antibodies according to manufacturers' instructions. The staining took place on the Omnis from Agilent™ (Agilent Technologies, Glostrup, Denmark) utilizing the EnVision Flex+ detection kit (GV800) or on the Ventana BenchMark Ultra from Roche™ (Roche Diagnostics, Hvidovre, Denmark) utilizing the UltraView/OptiView detection kit (760-500/760-700). The sections were counterstained with haematoxylin.

Data were reviewed by a radiologist (T.S.K.) and a pathologist (B.H.F.) with results documented below. Data collection was approved by the Danish Data Protection Agency (RH-2015-07, nr. 03616) and patients' consent.

## Results

Within the period of our study, 1575 patients underwent surgery for tumors of the pancreas of whom 15 patients had an SPN (Table 2). Of the 15 patients, 10 were diagnosed during the past 5 years. Patients' median age was 40 (range 10–87) years, 12 patients were females (80%), and 3 patients were children or adolescent aged 10, 12, and 15 years. Ten patients including all minors had abdominal symptoms with pain or discomfort; one patient also had hematemesis due to tumor growth into the duodenum. SPN was discovered incidentally in five patients during examination for other diseases.

Median tumor size was 5 cm (range 2–16 cm). Abdominal symptoms were not related to tumor size. Six tumors were in the head, six in the body, and three the tail of the gland.

Preoperative CT scan or biopsy was diagnostic in 11 patients. CT scan showed characteristic radiologic signs of an SPN in eight patients (Figure 1). MRI (four patients), <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG-PET) (two patients), and <sup>111</sup>In-octreotide scintigraphy (one patient) did not contribute further to the diagnosis.

Two patients (numbers 4 and 12, Table 2) had radiological signs of a neuroendocrine tumor with enhancement of contrast uptake in the arterial phase. The first of the two patients had a tumor with invasion into the duodenum and encasement of the superior mesenteric vein, an 8 cm × 5 cm large liver metastasis with involvement of the second and third hepatic segment and metastases to 3 out of 16 lymph

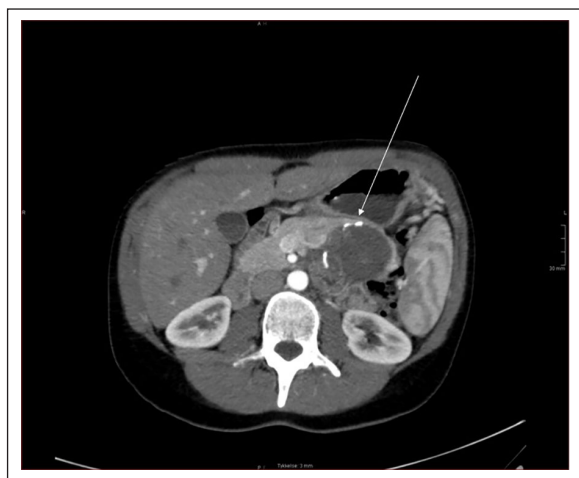
**Table 2.** Clinical data of 15 patients with solid pseudopapillary tumor of the pancreas.

Patient	Age	Tumor site	Tumor size (cm)	Metastases	Radiographic appearance	Calcification	Preoperative diagnosis made		Operation	Survival (months)
							From CT/MRI	From biopsy		
1	30	Head	6		Cystic/solid		No	Yes	PD	204.9
2 <sup>a</sup>	23	Body	5		Cystic/solid	Yes	Yes	Yes	DP	106.1
3	15	Tail	9		Cystic/solid		No	No	DP	110.9
4	68	Head	7	Nodes and liver	Cystic/solid		No	Yes	PD <sup>b</sup>	89.7
5	40	Tail	5		Cystic/solid	Yes	Yes	Yes	DP	83.2
6	12	Head	5		Cystic/solid		Yes	Yes	PD <sup>b</sup>	69.2
7	68	Head	15		Cystic	Yes	Yes	nd	PD	43.8
8	41	Head	3		Cystic	Yes	Yes	Yes	PD	40.3
9 <sup>a</sup>	73	Body	—				No	nd	PD	39.1
10	87	Tail	16		Cystic/solid	Yes	Yes	Yes	nd	38.1
11	30	Body	7		Cystic/solid	Yes	Yes	Yes	DP	31.6
12	44	Body	4		Solid		No	nd	DP	29.0
13	21	Body	15		Cystic/solid		No	Yes	PD	22.3
14 <sup>a</sup>	10	Head	6		Cystic/solid		Yes	nd	PD	17.5
15	51	Body	2		Cystic/solid		No	nd	DP	13.0

PD: pancreaticoduodenectomy; DP: distal pancreatectomy; nd: not done; CT: computed tomography; MRI: magnetic resonance imaging.

<sup>a</sup>Male.

<sup>b</sup>Vascular resection.



**Figure 1.** A 30-year old woman with a solid pseudopapillary neoplasm of the pancreas. Axial contrast-enhanced arterial phase CT image shows a well-defined heterogenous mass in the tail of the pancreas with peripheral calcifications (arrow).

nodes. An <sup>111</sup>In-octreotide scintigraphy showed an increased activity of the pancreatic tumor (Grades 3–4) but neither of the liver metastasis (Grade 3 uptake, equivalent to physiologic liver uptake) nor of the lymph nodes.

A preoperative biopsy was obtained in 10 patients, and nine biopsies including three fine-needle aspiration (FNA) were diagnostic. In one patient (number 4), the diagnosis was suggestive of a pseudopapillary neoplasm alternatively

a neuroendocrine tumor and in another patient the result was inconclusive.

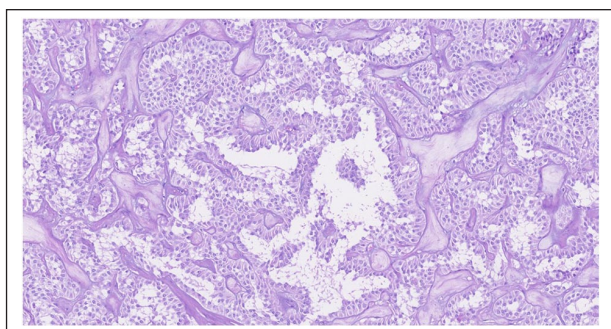
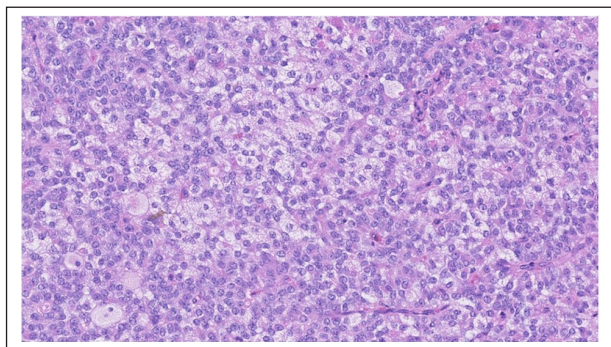
Fourteen patients underwent operation, one patient aged 87 years was not operated due to old age. Eight patients had a pancreaticoduodenectomy, one with concomitant resection of a liver metastasis, and six patients had a distal pancreatectomy with splenectomy. Resection of the porto-mesenteric vein was performed in two patients including the patient with metastatic disease, and one patient (number 14) had an additional resection of the right colon due to inflammatory adhesions between tumor and the bowel. One patient (number 9) had a total gastrectomy and a pancreaticoduodenectomy due to a gastric cancer. The tumor infiltrated near to the pancreas and at the time of operation the assessment was that the tumor had spread to the gland. Histopathological examination showed, however, that the tumor in the pancreas was separate from the gastric adenocarcinoma and was in fact an SPN.

There was only one tumor (patient number 4) expressing gross malignant features with infiltration into the duodenum, lymph node, and liver metastases. This was the only tumor with a high proliferation rate (ki67 23%). The primary tumor and the metastases revealed same morphology and immunohistochemical characteristics. Only one tumor showed focal perineural invasion (patient number 15), while no tumor showed vascular invasion of tumor cells. The resected mesenteric veins and the transverse colon only showed inflammatory reaction.

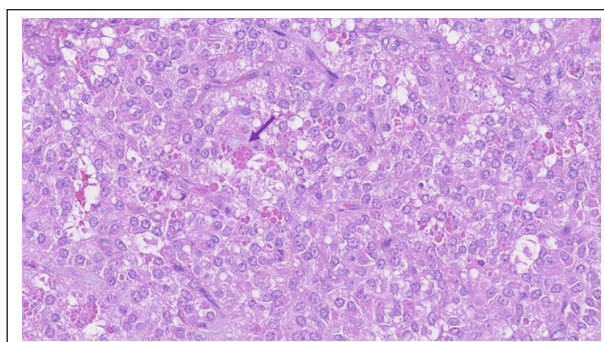
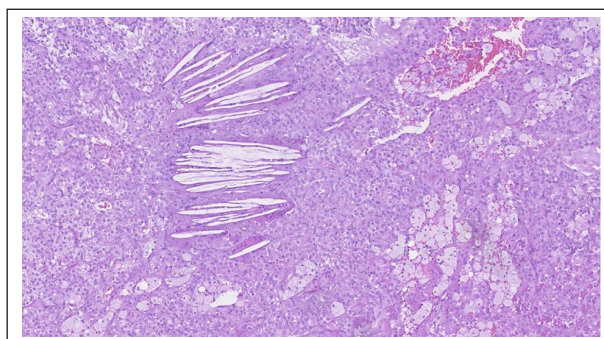


**Table 3.** Histologic analysis of 15 solid pseudopapillary tumors.

Patient	Pseudopapilla	Clear cells	Calcification	Cholesterol clefts	Foamy macrophages	Vacuolated cytoplasm	Eosinophile globules	High-grade transformation	Vascular invasion	Perineural invasion
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
2 <sup>a</sup>	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
3	Yes	No	No	No	Yes	No	No	No	No	No
4	Yes	No	No	No	No	Yes	No	Yes	No	No
5	Yes	No	No	No	No	Yes	Yes	No	No	No
6	Yes	No	No	No	Yes	Yes	Yes	No	No	No
7	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
8	Yes	Yes	Yes	No	No	Yes	No	No	No	No
9 <sup>a</sup>	Yes	No	No	No	Yes	Yes	Yes	No	No	No
10	Yes	No	No	No	No	Yes	Yes	No	No	No
11	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No
12	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No
13	Yes	Yes	No	No	Yes	No	Yes	No	No	No
14 <sup>a</sup>	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No
15	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes

<sup>a</sup>Male.**Figure 2.** Solid pseudopapillary neoplasm of the pancreas with characteristically histologic morphology. Pseudopapilla with hyaline stroma, HE  $\times 100$ .**Figure 3.** Tumor cells with vacuolated cytoplasm, HE  $\times 175$ .

Tumor pathology was similar in adults and children (Table 3). Pseudopapilla formation and vacuolated cytoplasm with eosinophilic globules were common findings followed by cholesterol clefts and the presence of foamy

**Figure 4.** Eosinophile globules marked by arrow, HE  $\times 200$ .**Figure 5.** Cholesterol and foamy macrophages, HE  $\times 80$ .

macrophages and clear cells (Figures 2–5). Most tumors showed immunohistochemically activity for vimentin, CD10, and  $\beta$ -catenin as well as  $\alpha 1$ -antitrypsin and  $\alpha 1$ -antichymotrypsin. Activity of the neuroendocrine marker synaptophysin was also a common finding while focal chromogranin activity was seen in two tumors (Table 4).

**Table 4.** Immunohistochemic analysis of 15 solid pseudopapillary tumors.

Patient	Chromogranin	Synaptophysin	Progesteron	Vimentin	CD10	CD56	Cyclin DI	β-catenin	α I-antitrypsin	α I-antichymotrypsin
1	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
2 <sup>a</sup>	Yes	Weak	—	Yes	—	Yes	—	—	Yes	Yes
3	Weak	Weak	Yes	—	Yes	Yes	—	—	—	—
4	Yes	Yes	No	Yes	No	—	—	No	Yes	Yes
5	Weak	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Weak	Yes	Yes	Yes	—	—	—	—	No	—
7	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	No	Weak	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9 <sup>a</sup>	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No
10	No	Yes	Yes	Yes	Yes	Yes	—	Yes	—	—
11	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—
13	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14 <sup>a</sup>	No	No	Yes	Yes	Yes	Yes	Yes	Yes	—	Yes
15	No	Yes	—	Yes	Yes	—	—	Yes	—	Yes

<sup>a</sup>Male—not done.

In one patient (number 4), an electron microscopy was needed to differentiate between a neuroendocrine tumor and SPN, and in the remaining patients, the final diagnosis was made by histopathologic examination.

There were no postoperative medical complications. Two patients had surgical complications. One patient had a pancreatic leakage after a distal pancreatectomy, and the fistula was treated conservatively by drainage. The other patient had a bowel fistula from his ileotransversostomy after a concomitant colonic resection. The fistula was resected with re-anastomosis. One patient had a late complication with a stricture of the hepaticojejunostomy 6 years after her operation, and a neo-hepaticojejunostomy was performed after abortive attempts to dilate the anastomosis with transhepatic (P.T.C.) balloon catheter. All 15 patients are still alive 13.0–196.8 months (median 40.3 months) after diagnosis, and the 14 operated cases without recurrence.

## Discussion

The SPN of the pancreas is a special entity as it has no resemblance to other pancreatic tumors. There have been speculations that the tumor cells have another origin than from the pancreas.<sup>7</sup> Since SPN is mainly seen in females, it has been hypothesized that it develops from displaced cells from the ovarian genital ridge, which is close to the primordial pancreas, or from pluripotent embryonic cells in the pancreas under influence of female hormones.

Several papers and casuistic communications on SPN have been published since the first description in 1933 including two large-scale reviews of English-written papers one covering the period from 1933 to 2003 (718 patients)<sup>8</sup> and the other from 1961 to 2012 (2744 patients).<sup>2</sup> This review also includes reference to 553 patients published in

Chinese papers between 1996 and 2009.<sup>9</sup> The number of patients with SPN recorded at our hospital during a study period of almost 18 years conforms to the number in a Swedish review of 16 cases from a catchment area of the same size as ours found between 1991 and 2010 and thus reflects the seldom occurrence of SPN in Scandinavia.<sup>10</sup> In one paper from Egypt<sup>11</sup> and another from Israel,<sup>12</sup> the number of SPN was higher with relation to total number of operated pancreatic tumors, 24/765 vs 32/1320 patients, respectively, than in the two Scandinavian studies.

As expected, we found a clear female preponderance among the patients, but the median age of 40 years was higher than the average age of 22.0, 27.2, and 28.5 years reported in the three large reviews above.

Most patients present with pain or non-specific abdominal symptoms, but tumor may also be indolent and, therefore, attain a considerable size before it is diagnosed. Jaundice or obstruction of the main pancreatic duct are uncommon, and clinical biochemistry is uncharacteristic and there are no useful tumor markers in plasma.<sup>8</sup>

Over the last decade, the number of reported SPN has increased concurrently with the more frequent use of CT scan and MRI. Ten of our patients were diagnosed during the last 5 years, but only five patients were found incidentally while the remaining patients had abdominal symptoms.

We found an almost equal distribution of tumors in the head or the body and tail, while location in the body and tail is reported to occur in about 60% of cases.<sup>2,8</sup> Median tumor diameter at diagnosis was 5 cm which is in accordance with the reported size of 6.0–8.6 cm. The gross anatomy typically reveals an encapsulated tumor with cystic degeneration and hemorrhage. Smaller tumors tend to be more solid while larger tumors are friable as they develop cystic degeneration and bleeding with growth.

Ultrasonography, CT scan, and MRI generally show the same features with an encapsulated tumor consisting of solid and cystic components, occasionally with rim-like calcifications in the capsule as well as intraparenchymatous calcifications.<sup>13,14</sup> The lesion has well defined margins often without dilatation of the pancreatic duct. Ultrasonography demonstrates various echogenic and hypoechogenic components, CT scan components of various density, and MRI lesions with a high-signal intensity on T1 and low signal intensity on T2 series representing hemorrhagic areas.<sup>14</sup> Angiographically, the tumor is usually found to be avascular or hypovascular. None of the radiological features, however, are characteristic of SPN, and the finding can also be seen in other pancreatic tumors especially cystic neuroendocrine tumors and pancreatoblastoma. The <sup>18</sup>F-FDG-PET varies in activity since tumor cells may have a high as well as a low metabolism.<sup>15</sup>

SPN is a cellular neoplasm with cells arranged in several layers around fibrovascular stalks, giving rise to the pseudopapillary structure. The histologic presence of a pseudopapillary architecture, hyaline globules, cholesterol clefts, foamy macrophages, and nuclear grooving with the absence of neuroendocrine (salt-and-pepper) chromatin are characteristic of a SPN.<sup>16,17</sup> The ultrastructure consists of non-desmosome-like junctions and electron-dense granules that may contain  $\alpha$ -1 antitrypsin.<sup>16</sup>

Immunohistochemically, SPN shows an abnormal staining pattern with both nuclear and cytoplasmic positivity for  $\beta$ -catenin and loss of E-cadherin from the cytoplasmic membrane.<sup>18,19</sup> Other common positive markers include progesterone receptor,  $\alpha$ -1 antitrypsin receptor, and CD10.<sup>20</sup>

SPNs often express immunoreactivity for the neuroendocrine markers synaptophysin and neuron-specific enolase and less common chromogranin. If the histologic and immunohistochemical appearance are not sufficiently characteristic to be diagnostic, electron microscopy may be helpful.

Common differential diagnoses are pancreatoblastoma, acinic cell tumor, and neuroendocrine tumor, which radiographically as well as immunohistochemically bear several similarities.<sup>21,22</sup> Nuclear and cytoplasmic  $\beta$ -catenin expression is reported in pancreatoblastoma, but the histologic appearance with cells formatting so-called squamoid corpuscles and dense bands of fibrous stroma are characteristic and different from SPN.<sup>23</sup> Pancreatoblastoma is most common in children and, contrary to SPN, has a male preponderance. Acinic cell tumors are rare in children but have a histologic appearance that resembles pancreatoblastoma but without squamoid corpuscles. Neuroendocrine tumors (islet-cell tumors) may be functioning with hormone secretion or non-functioning. Neuroendocrine tumor markers like synaptophysin, chromogranin, and CD56 may be variably expressed in SPN.

The differentiation between non-functioning neuroendocrine tumors and SPNs may be difficult. Two of our patients (numbers 4 and 12, Table 1) had a tumor with a

radiological appearance of a neuroendocrine tumor. Tumor from the second patient had synaptophysin activity but also showed activity for vimentin, CD10,  $\alpha$ 1-antitrypsin,  $\alpha$ 1-antichymotrypsin, and especially  $\beta$ -catenin, which was decisive for the SPN diagnosis.

The diagnosis of patient number 4 was more difficult. A preoperative biopsy from the primary tumor and the liver metastasis suggested a pseudopapillary tumor. <sup>111</sup>In-octreotide scintigraphy showed activity of the pancreatic tumor but neither of the liver metastasis nor of the metastatic lymph nodes. Although <sup>111</sup>In-octreotide activity has a high specificity for neuroendocrine tumors, activity may be found in other neoplasms as well as in non-neoplastic conditions.<sup>24</sup> Postoperative pathologic analysis of the primary tumor and metastasis showed activity of synaptophysin and chromogranin A without reaction for CD10 and  $\beta$ -catenin. The Ki67 was 23% of the pancreatic tumor and 2% of the liver metastasis, thus the differential diagnosis could be a neuroendocrine carcinoma. However, the tumor had a positive staining for vimentin,  $\alpha$ 1-antitrypsin, and  $\alpha$ 1-antichymotrypsin which are characteristic of an SPN. Electron microscopy could demonstrate dense bodies, but neither neurosecretory vesicles nor cytoplasmic annulated lamellae or junctions, and the final diagnosis was an SPN.

The differentiation between SPN with malignant and benign potential is difficult as signs of malignant behavior except from metastases are controversial.<sup>25</sup> According to the WHO classification, clear criteria of malignancy are vascular and nerve sheath invasion or lymph node and liver metastases in which cases tumor is designated as solid-pseudopapillary carcinoma.<sup>6</sup> Tumor size larger than 5 cm and growth into the capsule and out into peripancreatic tissue have all been related to malignancy.<sup>2,26</sup> Only one of our patients had metastatic disease with liver and lymph node metastases and a tumor infiltrating the duodenum. Seven patients had a tumor size larger than 5 cm but none have had recurrence so far. One tumor had perineural growth while the two cases with involvement of the mesenteric vessels and adhesion to the colon in another patient were due to inflammatory reaction and not tumor infiltration.

The only curative treatment is radical surgery with free resection margins,<sup>11,12,27</sup> and adjuvant oncologic therapy has no impact on survival. Due to the localized growth of STN, this is possible in most cases. Local tumor infiltration or metastatic disease is not a contraindication for operation since radical resection including all metastatic tissue may result in long-term survival and cure. The overall 5-year survival rate is more than 95.0% in large-scale reviews and the recurrence rate up to 6.6%.<sup>2,8,9</sup>

One pediatric study falls outside these results.<sup>28</sup> Among 41 patients with a median age of 13 years, seven (17.1%) had relapse from 33 to 94 months after operation, two had local recurrence, and five intraperitoneal dissemination. The authors found that the only risk factors of relapse were a positive resection margin and an age under 13.5 years. The first factor is not surprising while the last may reflect



the outcome of less aggressive surgery in minors. There is no evidence that children should have a higher recurrence rate than adults.

Primary metastatic disease as well as recurrence have been treated according to different oncologic protocols including 5-FU, S-1, gemcitabine, sunitinib, and transarterial embolization of liver metastases (TACE).<sup>29,30</sup> However, the results are casuistic, and the general opinion is that oncologic treatment has a limited effect on SPN which calls for aggressive surgical resection including metastases and in case of recurrence.

In conclusion, pancreatic SPN is a rare neoplasm with a malignant potential but a favorable prognosis. Radical surgery is associated with cure or long-term survival even in case of metastases. Recurrence after radical surgery is seldom and should be treated surgically, since oncologic treatment has limited effect. Thorough histologic analysis with immunohistochemistry is important to differentiate SPN from pancreatoblastoma, acinic, and neuroendocrine tumors.

### Ethical approval

Ethical approval for reporting case series is not required by Danish law.

### Informed consent

Data collection was approved by the Danish Data Protection Agency (RH-2015-07, nr. 03616) and patients' consent.

### Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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